New 4-Pyridyl Nonaflates as Precursors for Push–Pull Solvatochromic Dyes

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Abstract: 2,6-Disubstituted 4-pyridyl nonaflates including methyl, phenyl, 2-thienyl and 2-furyl groups were prepared by cyclocondensation reactions of the appropriate β-ketoenamides. Palladium-catalyzed cross-couplings (Suzuki–Miyaura, Mizoroki–Heck and Sonogashira reactions) led to buildings blocks that are direct precursors for the envisioned synthesis of push–pull solvatochromic dyes.

Key words: enamides, pyridines, cyclocondensations, nonaflates, cross-couplings

Pyridinium phenolates are the most prominent members in the class of solvatochromic push–pull dyes, a group of molecules that exhibits outstanding changes in their spectroscopic properties when the polarity of the surrounding medium is modified.[1] In particular, their extreme sensitivity in the UV/Vis–IR region, made them convenient probes to explore very different chemical environments, such as pure solvents and solvent mixtures,[2] micellar,[2b,3] dendrimer[4] and electrolyte solutions.[5]

Figure 1 shows three important examples of solvatochromic pyridinium phenolates, $E_T(30)$ or Reichardt's betaine **1**,[6] Brooker's merocynine (**2**)[7] and POMP (**3**) [4-(*N*-methyl-4-pyridinio)phenolate].[8] Besides their spectroscopic properties that have been subject of experimental and theoretical investigations,[9] they represent adequate examples of how this class of compounds is generally prepared in literature. In all cases, the precursors of the donor (phenolate) and the acceptor (pyridinium) moieties are prepared separately and subsequently linked. ANROC reactions (Addition of the Nucleophile, Ring Opening, and Ring Closure) of pyrylium salts using suitable aminophenols as nucleophiles have been used to prepare several compounds similar to **1**.[10] Alternatively compounds like **2** can be accessed by condensation reactions between N-alkylated pyridinium salts and hydroxybenzaldehydes.[11] Finally, Suzuki–Miyaura cross-coupling reactions between 4-pyridineboronic esters and bromophenols allowed the access to a library of compounds like **3**.[8] This last approach has been less explored and represents a rapid and versatile path to new and highly functionalized solvatochromic dyes if suitable pyridine derivatives for palladium-catalyzed reactions can be easily prepared.

In recent years, our group has developed a new and flexible procedure for the preparation of highly functionalized 4-hydroxypyridines by means of a trimethylsilyl trifluoromethanesulfonate/base-promoted intramolecular condensation of β-ketoenamides.[12] Smooth O-nonaflation of the resulting 4-hydroxypyridines and subsequent functionalizations by palladium-catalyzed cross-coupling reactions led to a broad range of specifically substituted pyridine derivatives.[13] In the present report, we focus on the preparation of 2,6-disubstituted 4-pyridyl nonaflates and their palladium-catalyzed couplings for the flexible preparation of a series of precursors for pyridine-based solvatochromic push–pull dyes.

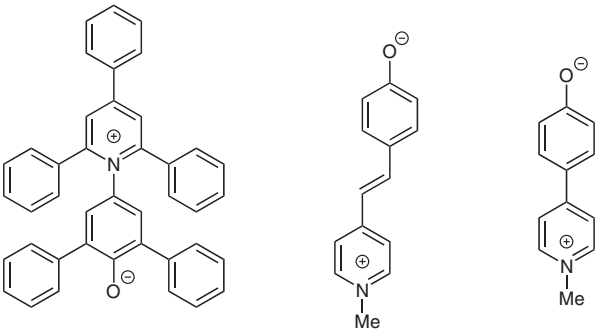

Figure 1 Prominent members of the family of solvatochromic pyridinium phenolate dyes

The synthetic sequence starts with the preparation of β-ketoenamines **6** employing three different methods (Scheme 1). The condensation reaction of 1,3-diketones with aqueous ammonia in the presence of catalytic amounts of SiO_2[14] represents a simple and economical procedure for the amination of symmetrical compounds such as **4** giving intermediate **6a** (R^1 = Me), but it cannot be applied for the regioselective preparation of compounds **6b**–**d** ($R^1 \neq$ Me). For that reason enamines **6b**–**d** were prepared by alternative methods. The hydrogenolysis of 5-methyl-3-phenylisoxazole (**5**) in the presence of Raney-Nickel at room temperature provided β-ketoenamines **6b** (R^1 = Ph) in good yield.[15] β-Ketoenamines **6c**,**d** (R^1 = 2-thienyl or 2-furyl) were prepared by treatment of acetone with sodium hydride in presence of 2-furancarbonitrile or 2-thiophenecarbonitrile under reflux conditions (see Supporting Information for details). Surprisingly, this simple reaction did not provide the desired products when nitriles such as benzonitrile or 2-chloro- or 4-chloropyridyl carbonitrile derivatives were employed, giving only traces of hydrolyzed nitriles as products even after prolonged reaction times. By N-acylation of β-ketoenamines **6a**–**d** with different carboxylic acid chlorides in presence of Et_3N, the

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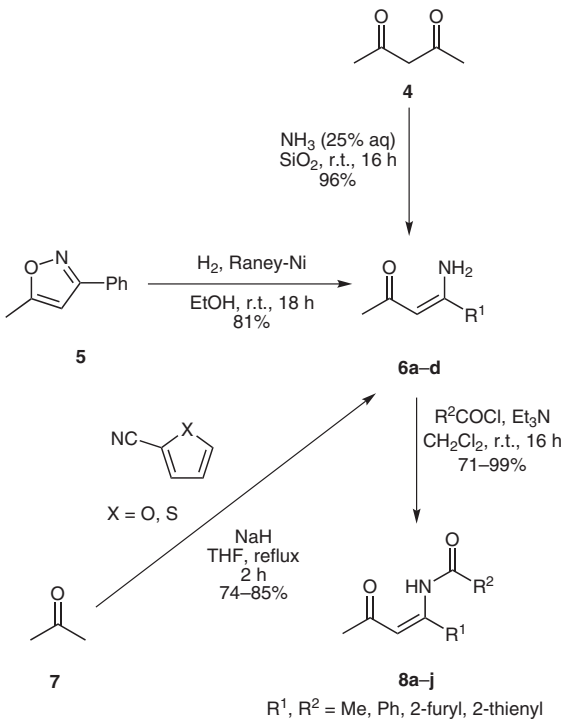
required β-ketoenamides **8a–j** were obtained in good yields (Scheme 1).

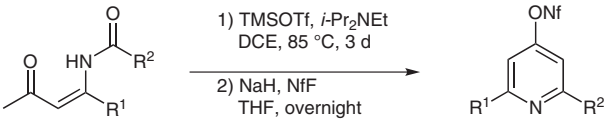


Scheme 1 Preparation of β-ketoenamines **6a** (R^1 = Me), **6b** (R^1 = Ph), **6c** (R^1 = 2-thienyl), and **6d** (R^1 = 2-furyl) and β-ketoenamides **8a–j** (for substituents R^1 and R^2 of compounds **8**, see Table 1)

The CH-acidic methyl ketone moiety in compounds of type **8** is susceptible to undergo an intramolecular aldol-type condensation reaction with the amide carbonyl moiety upon treatment with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of *i*-Pr_2NEt. The cyclized primary 4-pyridinols were not isolated and purified but directly subjected to O-nonaflation employing nonafluorobutanesulfonyl fluoride (NfF) to provide the desired 4-pyridyl nonaflates **9** in moderate to good overall yields (Table 1).

Since our strategy for the preparation of pyridinium phenolate solvatochromic dyes proposes 4-pyridyl nonaflates as key intermediates, different palladium-catalyzed cross-coupling reactions were carried out with anisole derivatives that serve as a latent phenolate donor. It was expected that the anisole moiety can easily be demethylated in the resulting pyridine derivatives.[16] Suzuki–Miyaura (Scheme 2), Heck–Mizoroki (Scheme 3) and Sonogashira (Scheme 4) coupling reactions of 4-pyridyl nonaflates **9a–d** with 4-methoxyphenylboronic acid, 4-methoxystyrene and 4-ethynylanisole, respectively, provided the expected 4-(4-methoxyphenyl)pyridines **10**, 4-(4-methoxystyryl)pyridines **11** and 4-[(4-methoxyphenyl)ethynyl]pyridines **12** in good yields.

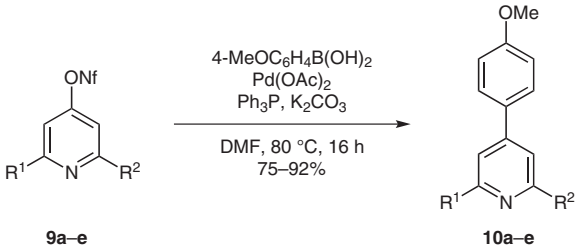
Table 1 TMSOTf/Base-Promoted Cyclocondensations of β-Ketoenamides **8a–j** and Subsequent O-Nonaflation Reactions[a]



8a–j **9a–j**

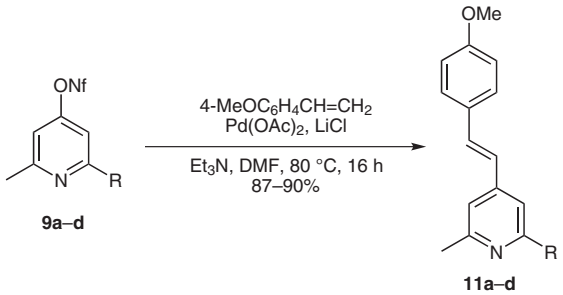
Entry	**8**	R^1	R^2	**9**	Yield (%)[b]
1	**8a**	Me	Me	**9a**	32
2	**8b**	Me	Ph	**9b**	83
3	**8c**	Me	2-thienyl	**9c**	62
4	**8d**	Me	2-furyl	**9d**	69
5	**8e**	Ph	Ph	**9e**	78
6	**8f**	2-thienyl	2-thienyl	**9f**	74
7	**8g**	2-thienyl	Ph	**9g**	73
8	**8h**	2-furyl	Ph	**9h**	75
9	**8i**	2-furyl	2-thienyl	**9i**	75
10	**8j**	2-furyl	2-furyl	**9j**	71

[a] Reaction conditions: TMSOTf (5.0 equiv), *i*-Pr_2NEt (4.0 equiv), 1,2-dichloroethane (DCE) (*c* = 0.04 M), NaH (7.0 equiv), NfF (2.5 equiv); Nf = $SO_2C_4F_9$.
[b] Yields over two steps.



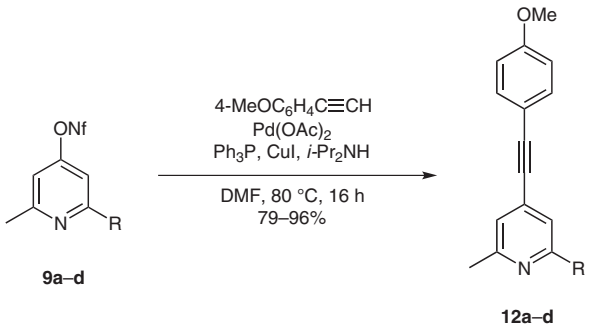
9a–e **10a–e**

Scheme 2 Suzuki–Miyaura couplings of 4-pyridyl nonaflates **9a–e** leading to 4-(4-methoxyphenyl)pyridines **10a** (R^1 = Me, R^2 = Me), **10b** (R^1 = Me, R^2 = Ph), **10c** (R^1 = Me, R^2 = 2-thienyl), **10d** (R^1 = Me, R^2 = 2-furyl), and **10e** (R^1 = Ph, R^2 = Ph)



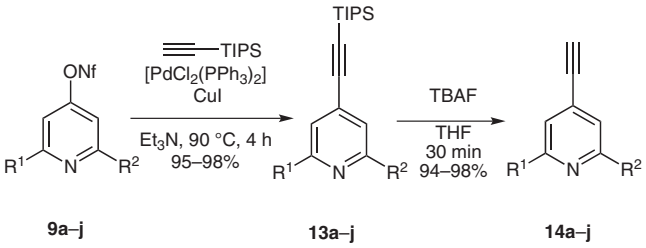
9a–d **11a–d**

Scheme 3 Heck–Mizoroki couplings of 4-pyridyl nonaflates **9a–d** leading to *(E)*-4-(4-methoxystyryl)pyridines **11a** (R = Me), **11b** (R = Ph), **11c** (R = 2-thienyl), and **11d** (R = 2-furyl)



Scheme 4 Sonogashira reactions of 4-pyridyl nonaflates **9a**–**d** leading to 4-[(4-methoxyphenyl)ethynyl]pyridines **12a** (R = Me), **12b** (Ph), **12c** (2-thienyl), and **12d** (2-furyl)

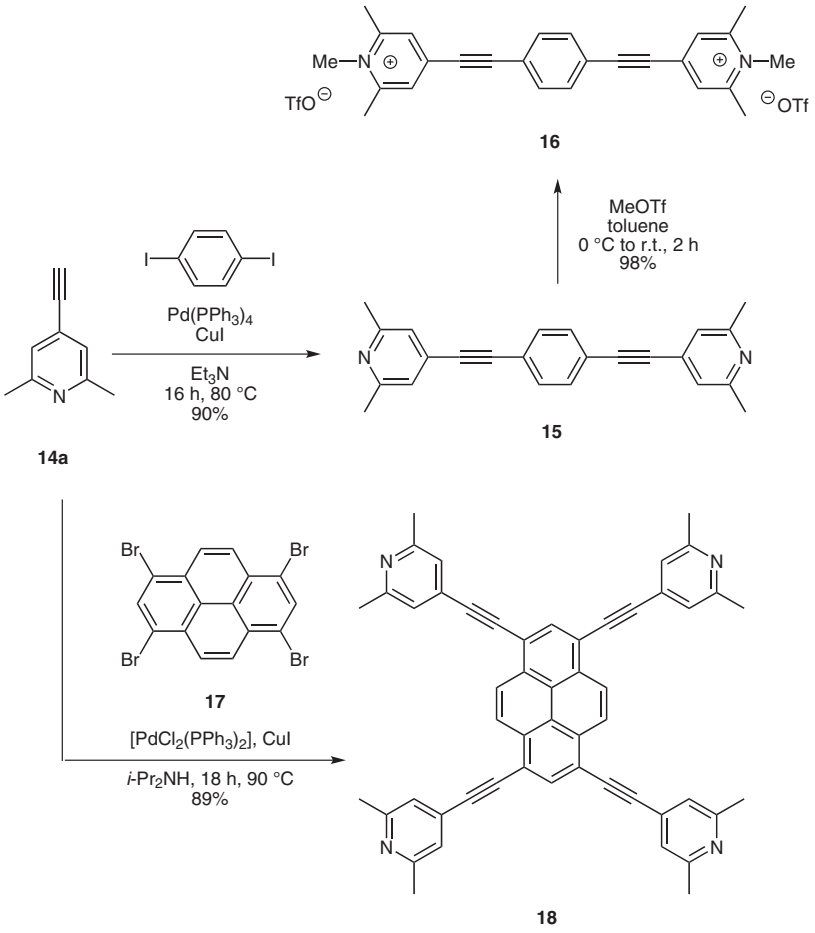
The above described coupling reactions clearly reveal the potential of this type of 4-pyridyl nonaflates for palladium-catalyzed processes. In addition, compounds **9a**–**j** were subjected to Sonogashira couplings with TIPS-acetylene. Subsequent treatment of the resulting products **13a**–**j** with tetra-*n*-butylammonium fluoride (TBAF) furnished the 2,6-disubstituted 4-ethynylpyridines **14a**–**j** in excellent overall yields (89–96%). These new building blocks are ready for further functionalizations leading to new pyridine derivatives (Scheme 5).



R1, R2 = Me, Ph, 2-thienyl, 2-furyl

Scheme 5 Sonogashira couplings of 4-pyridyl nonaflates **9a**–**f** leading to 4-ethynylpyridines **14a**–**j**

As an example of possible subsequent reactions, ethynylpyridine **14a** was subjected to Sonogashira reactions under standard conditions employing 1,4-diiodobenzene and 1,3,6,8-tetrabromopyrene (**17**) that led to new rigid chromophores **15** and **18** in high yields (Scheme 6). Compound **15** was smoothly N-methylated by methyl triflate to furnish bis(pyridinium) salt **16**.



Scheme 6 Sonogashira couplings of 4-ethynyl-2,6-dimethylpyridine (**14a**) leading to rigid chromophores **15**, **16** and **18**

In conclusion, nine new 2,6-disubstituted 4-pyridyl nonaflates were prepared and subsequently subjected to palladium-catalyzed cross-couplings (Suzuki–Miyaura, Heck–Mizoroki and Sonogashira reactions) leading to a series of 4-(4-methoxyphenyl)pyridine, 4-(4-methoxystyryl)pyridine and 4-[(4-methoxyphenyl)ethynyl]pyridine derivatives in good overall yields. These compounds are direct precursors for solvatochromic pyridinium-phenolate dyes. In addition, the prepared nonaflates were converted to 2,6-disubstituted 4-ethynylpyridine derivatives in excellent yields, providing new building blocks for further coupling reactions. The preparation of push–pull solvatochromic dyes from compounds **10**, **11** and **12** (by N-methylation, O-demethylation and deprotonation) and their photophysical properties, including their solvatochromic behavior will be published in a future report.

Reactions were generally performed under argon in flame-dried flasks and liquid components were added by syringe. Column chromatography was performed with silica gel (230–400 mesh, Macherey & Nagel). All yields refer to analytically pure samples. ^{1}H NMR [$CHCl_3$ (δ = 7.26), TMS (δ = 0.00) as internal standard], ^{13}C NMR spectra [$CDCl_3$ (δ = 77.0) as internal standard] and ^{19}F NMR spectra were recorded with Bruker (AC 500, VIII 700), Jeol ECX 400, or Jeol Eclipse 500 instruments in $CDCl_3$ solutions. Integrals are in accordance with assignments; coupling constants are given in Hz. All ^{13}C NMR spectra are proton-decoupled. ^{13}C NMR signals of Nf groups [$CF_3(CF_2)_3$] are not given since unambiguous assignment was not possible due to strong splitting by coupling with the ^{19}F nuclei. IR spectra were measured with a Jasco FT/IR-4100 spectrometer. HRMS analyses were performed with Varian Ionspec QFT-7 (ESI-FT ICRMS) and Agilent 6210 ESI-TOF instruments. The elemental analyses were recorded with Perkin-Elmer CHN-Analyzer 2400, Vario EL or Vario EL III instruments. Melting points were measured with a Reichert apparatus and are uncorrected. CH_2Cl_2 was purified with a MB SPS-800 dry solvent system and dry DMF was acquired from Across Organics. Unless stated otherwise all other solvents and reagents were purchased from commercial suppliers and were used without further purification. The preparation of compound **9a**[12k] and **9b**[12f] has been previously reported. Synthesis of the precursor β-ketoenamines **6c**,**d** and ketoenamides **8a**–**j** is described in detail in the Supporting Information.

TMSOTf-Promoted Cyclization of β-Ketoenamides and Subsequent Nonaflation; General Procedure 1

TMSOTf (5.0 equiv) was added dropwise to a stirred solution of the β-ketoenamide (1.0 equiv) and *i*-Pr_2NEt (4.0 equiv) in 1,2-dichloroethane (0.04 mol/L) under argon atmosphere. The resulting reaction mixture was stirred at 90 °C in a Schlenk flask equipped with a reflux condenser for 3 d. After cooling the reaction mixture to r.t., the solvent was carefully evaporated under reduced pressure. The resulting brown crude solid was dissolved in THF (~12 mL per mmol of β-ketoenamide) and transferred to a suspension of NaH (7.0 equiv, 60% in mineral oil) in a small amount of THF. After 30 min, NfF (2.5 equiv) was added and the mixture was stirred at r.t. overnight. Sat. aq NH_4Cl solution was slowly added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × ~50 mL per mmol of β-ketoenamide) and the combined organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The obtained crude product was purified by column chromatography on silica gel.

2-Methyl-6-(thiophen-2-yl)pyridin-4-yl Nonaflate (9c)

According to general procedure 1, (*Z*)-*N*-(4-oxopent-2-en-2-yl)thiophene-2-carboxamide (**8c**; 248 mg, 1.19 mmol) was treated with *i*-Pr_2NEt (0.83 mL, 4.76 mmol) and TMSOTf (1.08 mL, 5.95 mmol) in 1,2-dichloroethane (30 mL). The obtained crude 4-hydroxypyridine was treated with NaH (333 mg, 8.33 mmol) and NfF (0.53 mL, 2.98 mmol) in THF (15 mL). After workup, the obtained crude product was purified by column chromatography on silica gel (hexanes–EtOAc = 40:1) to provide compound **9c** (352 mg, 62%) as a light yellow oil.

IR (ATR): 3130–2920 (=C–H), 2855 (C–H), 1605 (C=C), 1575 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.62 (s, 3 H, CH_3), 6.92 (d, *J* = 2.1 Hz, 1 H, 3-H), 7.12 (dd, *J* = 5.1, 3.8 Hz, 1 H, Thio-4-H), 7.33 (d, *J* = 2.1 Hz, 1 H, 5-H), 7.44 (dd, *J* = 5.1, 1.1 Hz, 1 H, Thio-5-H), 7.60 (dd, *J* = 3.8, 1.1 Hz, 1 H, Thio-3-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 24.8 (q, CH_3), 108.0 (d, C-5), 113.2 (d, C-3), 125.9, 128.3, 129.0 (3 d, Thio-C-3, -C-4, -C-5), 143.3 (s, Thio-C-2), 154.9, 157.4, 162.0 (3 s, C-2, C-4, C-6).

^{19}F NMR ($CDCl_3$, 376 MHz): δ = –125.7, –120.8 (2 m_c, 2 F each, CF_2), –108.5 (t, *J* = 14.0 Hz, 2 F, CF_2), –80.6 (t, *J* = 9.4 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{14}H_9F_9NO_3S_2$ $[M + H]^+$: 473.9875; found: 473.9863.

Pd-Catalyzed Coupling of Pyridyl Nonaflates with 4-Methoxyphenylboronic Acid; General Procedure 2

Dry DMF (~7 mL/mmol) was transferred to a Schlenk flask charged with the 4-pyridyl nonaflate (1.0 equiv), $Pd(OAc)_2$ (6 mol%), Ph_3P (20 mol%), K_2CO_3 (1.0 equiv) and 4-methoxyphenylboronic acid (1.2 equiv) under argon atmosphere. The mixture was stirred at 80 °C for 16 h. After cooling to r.t., the mixture was diluted with water (~35 mL/mmol) and extracted with EtOAc (3 × ~50 mL/mmol). The combined organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The obtained crude product was purified by column chromatography.

4-(4-Methoxyphenyl)-2-methyl-6-(thiophen-2-yl)pyridine (10c)

According to general procedure 2, 2-methyl-6-(thiophen-2-yl)pyridin-4-yl nonaflate (**9c**; 400 mg, 0.85 mmol) was treated with $Pd(OAc)_2$ (12 mg, 0.05 mmol), Ph_3P (45 mg, 0.17 mmol), K_2CO_3 (118 mg, 0.85) and 4-methoxyphenylboronic acid (155 mg, 1.02 mmol) in DMF (6.0 mL). The obtained crude product was purified by column chromatography on silica gel (hexanes–EtOAc = 20:1) to provide compound **10c** (180 mg, 75%) as a yellow oil.

IR (ATR): 3030–2800 (=C–H, C–H), 1600 (C=C), 1515 (C=N), 1255 cm^{-1} (C–O–CH_3).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.62 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 6.99–7.03 (m, 2 H, Ar), 7.09–7.13 (m, 1 H, Thio-4-H), 7.19 (d, *J* = 1.5 Hz, 1 H, 3-H), 7.35–7.39 (m, 1 H, Thio-5-H), 7.59–7.65 (m, 4 H, Thio-3-H, Ar, 5-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 24.7 (q, CH_3), 55.5 (q, OCH_3), 113.8, 114.5 (2 d, C-3, Ar), 119.3, 121.3 (2 d, C-5, Ar), 127.3, 128.0, 128.3 (3 d, Thio-C-3, -C-4, -C-5), 130.9 (s, Thio-C-1), 137.6, 143.1 (2 s, C-4, Ar-C-4), 154.8, 158.9, 160.5 (3 s, C-2, C-6, Ar-C-1).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{16}NOS$ $[M + H]^+$: 282.0947; found: 282.0980.

Pd-Catalyzed Coupling of Pyridyl Nonaflates with 1-Methoxy-4-vinylbenzene; General Procedure 3

Dry DMF (~4.2 mL/mmol) was transferred to a Schlenk flask charged with the 4-pyridyl nonaflate (1.0 equiv), $Pd(OAc)_2$ (7 mol%), LiCl (5.0 equiv), Et_3N (2.1 mL/mmol) and 1-methoxy-4-vinylbenzene (6.0 equiv) under argon atmosphere. The mixture was stirred at 80 °C for 16 h. After cooling to r.t. the mixture was diluted with water (~21 mL/mmol) and extracted with EtOAc (~50 mL/mmol). The combined organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The obtained crude product was purified by column chromatography.

(*E*)-4-(4-Methoxystyryl)-2-methyl-6-(thiophen-2-yl)pyridine (11c)

According to general procedure 3, 2-methyl-6-(thiophen-2-yl)pyridin-4-yl nonaflate (**9c**; 400 mg, 0.85 mmol) was treated with $Pd(OAc)_2$ (12 mg, 0.05 mmol), LiCl (180 mg, 4.25 mmol), Et_3N (1.8 mL) and 1-methoxy-4-vinylbenzene (0.70 mL, 5.22 mmol) in DMF (3.6 mL). The obtained crude product was purified by column chromatography on silica gel (hexanes–EtOAc = 20:1) to provide compound **11c** (221 mg, 85%) as a yellow oil.

IR (ATR): 3010–2840 (=C–H, C–H), 1600 (C=C), 1510 (C=N), 1250 cm^{-1} (C–O–CH_3).

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.04 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 6.88 (d, *J* = 16.3 Hz, 1 H, PyC*H*=), 6.92 (d, *J* = 8.8 Hz, 2 H, Ar), 7.08–7.09 (m, 1 H, 3-H), 7.11 (dd, *J* = 5.1, 3.7 Hz, 1 H, Thio-3-H), 7.27 (d, *J* = 16.3 Hz, 1 H, PyCH=C*H*), 7.35–7.39 (m, 1 H, Thio-5-H), 7.47–7.52 (m, 3 H, Ar, Thio-3-H) 7.60–7.64 (m, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 24.6 (q, CH_3), 55.3 (q, OCH_3), 100.0, 108.6 (2 d, Thio-C-3, -C-4), 112.0, 113.2, 114.8, 118.8 (4 d, C-3, C-5, Ar, Py*C*H=), 124.7, 128.3, 129.0, 132.5 (s, 3 d, Ar, PyCH=*C*, Thio-C-5), 143.2, 146.0, 149.3 (3 s, C-2, C-4, C-6), 158.8, 160.0 (2 s, Thio-C-1, Ar-C-1).

HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{18}NOS$ $[M + H]^+$: 308.1104; found: 308.1113.

Pd-Catalyzed Coupling of Pyridyl Nonaflates with 1-Ethynyl-4-methoxybenzene; General Procedure 4

Dry DMF (~4.6 mL/mmol) was transferred to a Schlenk flask charged with the 4-pyridyl nonaflate (1.0 equiv), $Pd(OAc)_2$ (7 mol%), CuI (5 mol%), Ph_3P (25 mol%), *i*-Pr_2NH (2.3 mL/mmol) and 1-ethynyl-4-methoxybenzene (1.2 equiv) under argon atmosphere. The mixture was stirred at 80 °C for 16 h. After cooling to r.t., the mixture was diluted with water (~23 mL/mmol) and extracted with EtOAc (3 × ~50 mL/mmol). The combined organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The obtained crude product was purified by column chromatography.

4-[(4-Methoxyphenyl)ethynyl]-2-methyl-6-(thiophen-2-yl)pyridine (12c)

According to general procedure 4, 2-methyl-6-(thiophen-2-yl)pyridin-4-yl nonaflate (**9c**; 400 mg, 0.85 mmol) was treated with $Pd(OAc)_2$ (14 mg, 0.06 mmol), CuI (9 mg, 0.05 mmol), Ph_3P (56 mg, 0.214 mmol), *i*-Pr_2NH (2.0 mL) and 1-ethynyl-4-methoxybenzene (135 mg, 1.02 mmol) in DMF (4.0 mL). The obtained crude product was purified by column chromatography on silica gel (hexanes–EtOAc = 40:1) to provide compound **12c** (205 mg, 79%) as a yellow oil.

IR (ATR): 3030–2840 (=C–H, C–H), 2105 (C≡C), 1600 (C=C), 1500 (C=N), 1280 cm^{-1} (C–O–CH_3).

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.57 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 6.88−6.92 (m, 2 H, Ar), 7.09 (d, *J* = 1.2 Hz, 1 H, 3-H), 7.10−7.12 (m, 1 H, Thio-3-H), 7.38 (d, *J* = 5.1, 1.1 Hz, 1 H, Thio-4-H), 7.48−7.51 (m, 2 H, Ar), 7.54 (d, *J* = 1.2 Hz, 1 H, 5-H), 7.57−7.61 (m, 1 H, Thio-5-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 24.7 (q, CH_3), 55.4 (q, OCH_3), 86.1 (s, Py*C*≡), 113.9, 114.4 (s, d, Ar, PyC≡*C*), 100.3, 108.9 (2 d, Thio-C-3, -C-4), 113.0, 118.9, 119.5 (s, 2 d, Ar, C-3, C-5), 132.0, 132.9, 133.5 (s, 2 d, C-4, Thio-C-5, Ar), 157.0, 158.0, 159.3, 160.2 (4 s, C-2, C-6, Thio-C-1, Ar-C-1).

HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{16}NOS$ $[M + H]^+$: 306.0947; found: 306.0956.

Pd-Catalyzed Coupling of Pyridyl Nonaflates with TIPS-acetylene; General Procedure 5

Dry Et_3N (~3 mL/mmol) was transferred to a Schlenk flask charged with the 4-pyridyl nonaflate (1.0 equiv), $[PdCl_2(PPh_3)_2]$ (~5 mol%), CuI (~2.5 mol%), and triisopropylsilylacetylene (1.2 equiv) under argon atmosphere. The mixture was stirred at 80 °C for 4 h. After cooling to r.t., the mixture was diluted with water (~15 mL/mmol) and extracted with EtOAc (3 × ~30 mL/mmol). The combined organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The obtained crude product was purified by column chromatography.

2-Methyl-6-(thiophen-2-yl)-4-[(triisopropylsilyl)ethynyl]pyridine (13c)

According to general procedure 5, 2-methyl-6-(thiophen-2-yl)pyridin-4-yl nonaflate (**9c**; 70 mg, 0.15 mmol) was treated with $[PdCl_2(PPh_3)_2]$ (6 mg, 8 μmol), CuI (1 mg, 5 μmol), and triisopropylsilylacetylene (33 mg, 0.18 mmol) in Et_3N (0.5 mL). The obtained crude product was purified by column chromatography on silica gel (hexanes–EtOAc = 20:1) to provide compound **13c** (51 mg, 96%) as a yellow oil.

IR (ATR): 3200–2850 (=C–H, C–H), 2100 (C≡C), 1595 (C=C), 1535 (C=N), 1440, 1220 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.13–1.17 (m, 21 H, TIPS), 2.55 (s, 3 H), 7.04–7.06 (m, 1 H, 5-H), 7.09 (dd, *J* = 5.0, 3.7 Hz, 1 H, Thio-4-H), 7.37 (dd, *J* = 5.0, 1.2 Hz, 1 H, Thio-5-H), 7.45–7.48 (m, 1 H, 3-H), 7.59 (dd, *J* = 3.7, 1.2 Hz, 1 H, Thio-3-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 11.3, 18.7 (q, d, TIPS), 24.4 (q, CH_3), 95.8, 104.6 (2 s, TIPS-C≡C), 118.2, 123.7, 124.9, 127.7, 128.1 (5 d, C-3, C-5, Thio-C-3, -C-4, -C-5), 132.2 (s, C-4), 144.6 (s, Thio-C-2), 152.2, 158.6 (2 s, C-2, C-6).

HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{30}NSSi$ $[M + H]^+$: 356.1863; found: 356.1863.

TIPS-Deprotection of [(TIPS)ethynyl]pyridines; General Procedure 6

TBAF (~2.0 equiv) was transferred to a Schlenk flask charged with the [(triisopropylsilyl)ethynyl]pyridine (1.0 equiv) in dry THF (~2.0 mL/mmol) at r.t. under argon atmosphere. After 30 min, the reaction mixture was diluted with water (~10 mL/mmol) and extracted with CH_2Cl_2 (3 × 30 mL/mmol). The combined organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The obtained crude product was purified by flash chromatography.

4-Ethynyl-2-methyl-6-(thiophen-2-yl)pyridine (14c)

According to general procedure 6, 2-methyl-6-(thiophen-2-yl)-4-[(triisopropylsilyl)ethynyl]pyridine (**13c**; 50 mg, 0.14 mmol) was treated with TBAF (0.3 mL, 1 M in THF) in dry THF (0.3 mL). The obtained crude product was purified by flash chromatography on silica gel (hexanes–EtOAc = 20:1) to provide compound **14c** (27 mg, 97%) as a yellow oil.

IR (ATR): 3300–2860 (=C–H, C–H), 2095 (C≡C), 1595 (C=C), 1540 (C=N), 1460, 1220 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.52 (s, 3 H, CH_3), 3.24 (s, 1 H, CH), 7.02–7.04 (m, 1 H, 5-H), 7.04–7.09 (m, 1 H, Thio-4-H), 7.33–7.38 (m, 1 H, Thio-5-H), 7.48 (s, 1 H, 3-H), 7.52–7.56 (m, 1 H, Thio-3-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 24.4 (q, CH_3), 68.0 (s, *C*≡CH), 81.3 (d, C≡*C*H), 118.4, 123.7, 124.9, 127.8, 128.1 (5 d, C-3, C-5, Thio-C-3, -C-4, -C-5), 131.0 (s, C-4), 144.4 (s, Thio-C-2), 152.3, 158.7 (2 s, C-2, C-6).

HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{10}NS$ $[M + H]^+$: 200.0528; found: 200.0533.

1,4-Bis[(2,6-dimethylpyridin-4-yl)ethynyl]benzene (15)

Dry Et_3N (4.0 mL) was transferred to a Schlenk flask charged with the 4-ethynyl-2,6-dimethylpyridine (**14a**; 100 mg, 0.76 mmol), $Pd(PPh_3)_4$ (88 mg, 0.08 mmol), CuI (8 mg, 0.04 mmol), 1,4-diiodobenzene (302 mg, 0.92 mmol) under an argon atmosphere. The mixture was stirred at 80 °C for 16 h. After cooling to r.t., the mixture

was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The obtained crude product was purified by column chromatography on silica gel (hexanes–EtOAc = 10:1 → 10:1) to provide compound **15** (231 mg, 90%) as a light yellow solid; mp 171–173 °C.

IR (ATR): 3100–2920 (=C–H, C–H), 2120 (C≡C), 1600 (C=C), 1540 (C=N), 1440, 1400, 1215 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.51 (s, 12 H, CH_3), 7.05–7.07 (m, 4 H, 3-H, 5-H), 7.48–7.52 (s, 4 H, C_6H_4).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 24.5 (q, CH_3), 89.4 (s, Py-*C*≡C), 92.2 (s, Py-C≡*C*), 122.1, 123.0, 131.4, 131.9 (2 s, 2 d, C-4, C-3, C-5, C_6H_4), 158.0 (s, C-2, C-6).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{24}H_{21}N_2$ $[M + H]^+$: 337.1699; found: 337.1709.

4,4′-[1,4-Phenylenebis(ethyne-2,1-diyl)]bis(1,2,6-trimethylpyridin-1-ium) Triflate (16)

Methyl triflate (0.1 mL, 0.9 mmol) was slowly added to a Schlenk flask charged with 1,4-bis[(2,6-dimethylpyridin-4-yl)ethynyl]benzene (**15**; 100 mg, 0.30 mmol) in dry toluene (3.4 mL) at 0 °C under argon atmosphere. The reaction mixture was allowed to warm up to r.t. in 2 h, after filtration the crude product was washed with *n*-hexanes (2.0 mL) and EtOAc (2.0 mL). Compound **16** (195 mg, 98%) was obtained as a light yellow solid; mp <300 °C.

IR (ATR): 3080 (=C–H, C–H), 2125 (C≡C), 1630, 1460, 1260 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ = 2.80 (s, 12 H, CH_3), 4.03 (s, 6 H, NCH_3), 7.82, 8.09 (2 s, 3-H, 5-H, C_6H_4).

^{13}C NMR (DMSO-d_6, 126 MHz): δ = 21.7 (q, CH_3), 40.9 (q, NCH_3), 88.1 (s, Py-*C*≡C), 99.4 (s, Py-C≡*C*), 122.7, 128.7, 133.4 (s, 2 d, C_6H_4, C-3, C-5), 137.1 (s, C-4), 156.8 (s, C-2, C-6).

^{19}F NMR (DMSO-d_6, 471 MHz): δ = –77.6 (s, CF_3).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{28}H_{26}F_6N_2NaO_6S_2$ $[M + Na]^+$: 687.1029; found: 687.1002.

Anal. Calcd for $C_{28}H_{26}F_6N_2O_6S_2$ (664.6): C, 50.60; H, 3.94; N, 4.21; S, 9.65. Found: C, 50.60; H, 3.96; N, 4.21; S, 9.67.

1,3,6,8-Tetrakis[(2,6-dimethylpyridin-4-yl)ethynyl]pyrene (18)

Dry DMF (2.0 mL) was transferred to a Schlenk flask charged with 4-ethynyl-2,6-dimethylpyridine (**14a**; 75 mg, 0.57 mmol), $[PdCl_2(PPh_3)_2]$ (28 mg, 39 μmol), CuI (8 mg, 0.04 mmol), *i*-Pr_2NH (0.9 mL) and 1,3,6,8-tetrabromopyrene (**17**;[17] 49 mg, 0.095 mmol) under argon atmosphere. The mixture was stirred at 90 °C for 18 h. After cooling to r.t., the mixture was diluted with water (10 mL) and the resulting suspension extracted with EtOAc (1 × 10 mL, discarded). The remaining water phase was extracted with CH_2Cl_2 (ca. 40 × 30 mL) until no green extract was observed. The combined CH_2Cl_2 phases were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The obtained crude product was washed successively with benzene, hexanes and EtOAc (3.0 mL each). As residue, compound **18** (61 mg, 89%) was obtained as an orange solid; mp <300 °C.

IR (ATR): 3000–2920 (=C–H, C–H), 2110 (C≡C), 1600 (C=C), 1540 (C=N), 1440 cm^{-1}.

^1H NMR ($CDCl_3$, 700 MHz): δ = 2.64 (s, 24 H, CH_3), 7.27 (s, 8 H, 3-H, 5-H), 8.43 (s, 2 H, 2-H′, 7-H′), 8.70 (s, 4 H, 4-H′, 5-H′, 9-H′, 10-H′).

Due to the very poor solubility, the recording of a ^{13}C NMR spectrum was not possible.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{52}H_{39}N_4$ $[M + H]^+$: 719.3169; found: 719.3190.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are experimental procedures for the synthesis of compounds **6a**,**b**,**d**, **8a**,**b**,**d**–**j**, **9d**–**j**, **10a**,**b**,**d**,**e**, **11a**,**b**,**d**, **12a**,**b**,**d**, **13a**,**b**,**d**–**j**, **14b**,**d**–**j** as well as copies of NMR spectra for all new compounds.

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